Cholesterol Levels Decrease soon after Acute Myocardial Infarction

David Rott MD[1], Robert Klempfner MD[1], Ilan Goldenberg MD[1] and David Leibowitz MD[2]

[1]Cardiac Rehabilitation Institute, Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel
[2]Department of Medicine, Hadassah-Hebrew University Medical Center, Mt. Scopus, Jerusalem, Israel

ABSTRACT: **Background:** While earlier studies indicated that cholesterol levels decrease significantly after an acute myocardial infarction (MI), a more recent study refuted this observation.

Objectives: To assess changes in plasma lipid levels after onset of acute MI, and determine important predictors of lipid dynamics.

Methods: We prospectively measured lipid levels of patients who presented with an acute MI. Blood samples were drawn on admission to the hospital (day 1), after fasting at least 12 hours overnight (day 2), and on the 4th day of hospitalization (day 4).

Results: Of 67 acute MI patients, 30 were admitted for ST elevation MI (STEMI) and 37 for non-STEMI. Both total cholesterol and low density lipoprotein cholesterol (LDL-C) levels decreased significantly (by 9%) in the 24 hours after admission and by 13% and 17% respectively on day 4. High density lipoprotein cholesterol (HDL-C) levels as well as triglycerides did not change significantly. Independent predictors of LDL-C decrease were the presence of diabetes mellitus [odds ratio (OR) 6.73, $P = 0.01$), and elevated cardiac troponin T (cTnT) levels (OR 1.81, $P < 0.04$).

Conclusions: LDL-C levels decrease significantly after an acute MI. The reduction is correlated with cTnT levels. Diabetes is a strong independent predictor of LDL-C decrease. In acute MI patients only measurements taken within 24 hours of onset should be used to guide selection of lipid-lowering medication.

IMAJ 2015; 17: 370–373

KEY WORDS: low density lipoprotein cholesterol (LDL-C), HMG CoA reductase inhibitor, statin, myocardial infarction (MI), diabetes

Studies performed four decades ago demonstrated an early decrease of up to 50% in serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) within the first several days after acute coronary syndrome (ACS) [1,2]. More recent studies supported this observation by showing a significant although less pronounced drop of 10–20% [3-6]. The findings of the study by Pitt et al. [7] contradict these previous observations by showing only a modest and non-clinically relevant drop (3–5%) in lipid levels in the 4 days after an ACS. To clarify this issue we assessed changes in plasma lipid levels after onset of acute myocardial infarction (MI). In addition, we looked for factors associated with a larger magnitude of TC and LDL-C decrease.

PATIENTS AND METHODS

Lipid levels of 67 consecutive patients with an acute MI were prospectively measured. Of them, 30 were admitted for ST elevation MI (STEMI) and 37 for non-ST elevation MI (NSTEMI).

Blood samples were drawn on admission to hospital (day 1, fasting or non-fasting sample), after fasting at least 12 hours overnight (day 2), and on the 4th day of hospitalization (day 4, fasting sample). Serum levels of high density lipoprotein cholesterol (HDL-C), TC, and triglycerides (TG) were measured. The LDL-C was calculated by the Friedewald equation [8]. Levels of serum C-reactive protein (CRP) were also measured on day 1, 2 and 4.

Patients were diagnosed with acute MI based on the current universal definition of acute MI using cardiac troponin T (cTnT) as a marker for myocardial necrosis [9].

STATISTICAL ANALYSIS

Data are presented as mean ± SD. Comparisons between multiple experimental groups were made with one-way ANOVA. Comparisons between proportions were made with Fisher's exact test (two-tailed). In order to identify independent predictors of a clinically significant decrease in LDL-C (e.g., decrease of ≥ 10%) on day 2, a logistic regression model was constructed with the following prespecified covariates: age, cTnT, the presence of diabetes mellitus, gender and MI type (STEMI or NSTEMI). P values ≤ 0.05 were considered statistically significant. SPSS (version 20) was used for statistical analysis. The study protocol was approved by the institutional Helsinki Committee.

RESULTS

Characteristics of the 67 patients with acute MI are shown in Table 1. Mean age was 58 ± 13 years, 83% were males, 31% had diabetes, 49% had hypertension, 61% were smokers, 29% had a history of coronary disease, and 25% were taking an HMG coA reductase inhibitor (statin) prior to admission. None of

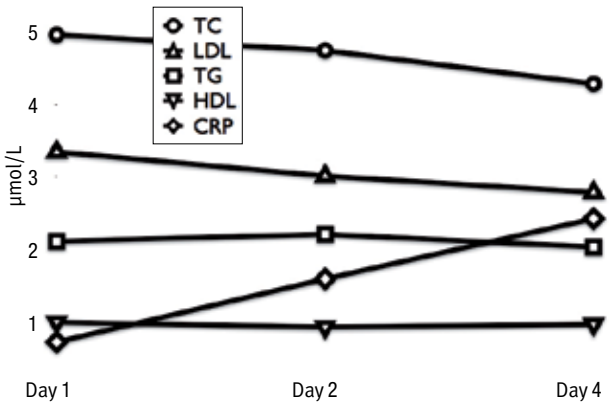
Table 1. Patient characteristics

	STE MI (n=30)	NSTE MI (n=37)	*P*
Age (mean ± SD)	59 ± 15.3	58.5 ± 11.4	NS
Female gender	13%	19%	NS
Diabetes	23%	38%	NS
Hypertension	40%	59%	NS
Smoking	80%	49%	NS
Previous MI	20%	35%	NS
Statin use*	16%	32%	NS
cTnT(mean ± SD)	2.0 ± 1.9	0.64 ± 0.63	‹ 0.0001

*Statin was used prior to admission

STEMI = ST elevation MI, NSTMI = non-STEMI, cTnT = cardiac troponin T

Figure 1. Changes in lipid profile parameters TC, LDL-C, HDL and triglycerides, and CRP, in the 4 days after an acute MI. The TC and LDL decreased significantly, HDL and TG levels did not change significantly, and CRP increased significantly



TC = total cholesterol, LDL-C = low density lipoprotein-cholesterol, HDL = high density lipoprotein, TG = triglyceride, CRP = C-reactive protein, MI = myocardial infarction

these characteristics were significantly different in both STEMI (30 patients) and NSTEMI (37 patients), except for peak cTnT which was significantly higher in STEMI patients. A trend for higher co-morbidities (diabetes, hypertension and previous MI) was seen for the NSTEMI patients.

All patients were clinically stable during the 4 day follow-up, and none of the patients received inotropes or blood transfusions.

As shown in Figure 1 and Table 2A, compared to day 1 there was a statistically significant decrease of 16% in TC and 21% in LDL-C levels on day 4: TC decreased from 4.99 ± 1.09 to 4.31 ± 1.0 ($P < 0.003$), and LDL-C decreased from 3.34 ± 1.04 to 2.77 ± 0.96 ($P < 0.01$). HDL-C levels as well as TG levels did not change significantly. As expected, CRP levels increased significantly from day 1 to day 4.

Table 2. Mean lipid values at each time point , and in statin-naïve compared to chronic statin-treated patients

A. All MI patients

Lipid parameter (µmol/L)	Day 1 (n=67)	Day 2 (n=67)	Day 4 (n=67)	*P* value
TC	4.99 ± 1.09	4.77 ± 0.97	4.31 ± 1.0	‹ 0.003
LDL	3.34 ± 1.04	3.07 ± 0.87	2.77 ± 0.96	‹ 0.01
HDL	0.94 ± 0.31	0.87 ± 0.28	0.91 ± 0.45	NS
TG	2.08 ± 1.36	2.18 ± 1.12	2.0 ± 0.73	NS
CRP	0.67 ± 0.78	1.55 ± 1.4	2.4 ± 1.5	‹ 0.01

B. STEMI patients

Lipid parameter (µmol/L)	Day 1 (n=30)	Day 2 (n=30)	Day 4 (n=30)	*P* value
TC	5.1 ± 1.0	4.78 ± 1.08	4.29 ± 0.98	‹ 0.01
LDL	3.45 ± 1.07	3.1 ± 1.05	2.74 ± 0.83	‹ 0.04
HDL	0.99 ± 0.34	0.89 ± 0.31	0.96 ± 0.58	NS
TG	1.92 ± 1.16	1.99 ± 0.97	1.87 ± 0.84	NS
CRP	0.63 ± 0.46	2.07 ± 1.8	3.4 ± 1.9	‹ 0.04

C. NSTEMI patients

Lipid parameter (µmol/L)	Day 1 (n=37)	Day 2 (n=37)	Day 4 (n=37)	*P* value
TC	4.9 ± 1.13	4.78 ± 0.89	4.32 ± 1.0	‹ 0.05
LDL	3.27 ± 1.0	3.06 ± 0.72	2.78 ± 1.08	0.09
HDL	0.89 ± 0.29	0.85 ± 0.27	0.85 ± 0.25	NS
TG	2.22 ± 1.53	2.31 ± 1.28	2.17 ± 0.64	NS
CRP	0.67 ± 0.52	1.1 ± 0.79	1.7 ± 0.8	‹ 0.03

D. Mean LDL levels of statin-naïve compared to chronic statin-treated patients

LDL levels (µmol/L)	Day 1	Day 2	Day 4	*P* value
Statin-naïve (n=50)	3.59 ± 1.01	3.3 ± 0.79	2.89 ± 0.97	‹ 0.001
Chronic statin (n=17)	2.76 ± 0.96	2.47 ± 0.96	2.45 ± 0.88	‹ 0.05

Values are mean ± SD

TC = total cholesterol, LDL = low density lipoprotein cholesterol, HDL = high density lipoprotein cholesterol TG = triglycerides, CRP = C-reactive protein

Fifty patients were statin-naïve (i.e., had never taken statins) at the time of admission, and 17 patients were on statin therapy prior to admission. All patients receiving statin therapy prior to admission received simvastatin 10, 20 or 40 mg/day. All 67 patients were prescribed atorvastatin, 40 mg, after admission. The first dose was given on day 2 in the evening. As expected, patients who were on a statin prior to admission had lower LDL-C levels compared to statin-naïve patients; however,

Table 3. Logistic regression model for predictors of › 10% decrease in LDL levels

	HR	CI 95%	*P* value
STEMI	1.74	0.53–5.77	0.36
Diabetes	6.73	1.63–27.85	0.01
cTnT (1 mmol increment)	1.81	1.01–3.24	0.04
Age (1 yr increment)	0.92	0.87–0.98	0.001
Male gender	0.61	0.12–3.26	0.57

OR = odds ratio, CI = confidence interval, STEMI = ST elevation myocardial infarction, cTnT = cardiac troponin T

LDL-C levels between day 1 and day 4 significantly decreased in both groups [Table 2D].

When separating the patients according to ST segment deviation, a similar statistically significant decrease in both TC and LDL-C was seen for STEMI patients [Table 2B]. In NSTEMI patients, a decrease in both TC and LDL-C was present as well; however, only the decrease in TC was statistically significant [Table 2C].

Logistic regression model [Table 3] identified the presence of diabetes mellitus as the strongest independent predictor of a clinically significant (e.g., ≥ 10%) decrease in LDL-C on day 2. In addition, higher cTnT levels were associated with a significant reduction in LDL-C levels on day 2. Gender and MI type (STEMI vs. NSTEMI) were not identified as significant predictors of LDL-C decrease, whereas higher age was associated with the reduced likelihood of a decrease in LDL-C.

DISCUSSION

Our observation is supported by previous studies mentioned above [1-6]. The magnitude of the decrease in lipid levels in our study is compatible with the results of more recent studies [3-6]. Our data demonstrated a decrease in TC and LDL-C in both STEMI and NSTEMI; however, the decrease was more significant in STEMI patients [Table 2], a finding compatible with the results of the LATIN study [6]. Moreover, our data showed that higher cTnT levels were associated with a more significant decrease in LDL [Table 3], suggesting that larger myocardial damage is associated with a more significant decrease in LDL levels. As shown in Table 3, diabetes mellitus was the strongest independent predictor of a more significant decrease in LDL.

LDL-C levels were significantly decreased regardless of previous statin use [Table 2D]. The fact that all patients were prescribed atorvastatin on the evening of day 2 clearly did not influence lipid levels measured on the morning of day 2 and would be unlikely to affect lipid levels on the morning of day 4, given that significant effects of a statin on lipid levels would be expected only at 2 weeks after initiation of treatment [10,11].

We suggest two explanations for the contradictory findings of the study by Pitt et al. [7]. Their study was a sub-study of the randomized LUNAR study. Eligibility for inclusion in the LUNAR study required admission to the hospital within 48 hours of onset of ischemic symptoms. Admission to the hospital was considered as day 1. Therefore, the "day 1" cholesterol level of a patient who started having symptoms 48 hours previously is equivalent to the level on day 2 or even day 3 in our study, as well as in the previous studies. If a significant number of the LUNAR study patients had been enrolled more than 24 hours after symptom onset, the nadir of TC and LDL-C may have been missed. In addition, our study included only patients with acute MI, whereas 23% of patients enrolled in the LUNAR study had unstable angina. The magnitude of the drop in lipid levels was higher in acute MI compared to unstable angina, as shown in the LATIN study [6]. The presence of a significant number of unstable angina patients may have contributed to the non-significant drop in lipid levels in the LUNAR study.

Possible mechanisms accounting for this decrease in TC and LDL-C in the presence of acute MI include the acute-phase response associated with up-regulation of LDL-C receptor activity [12]. In addition, stress-induced myocardial injury facilitates adrenergic mediated adipocyte lipolysis leading to free fatty acid mobilization, enhanced hepatic very low density lipoprotein (VLDL) secretion, TG elevation, and alteration in LDL and HDL particle composition [13,14].

Our results showing that higher cTnT levels were associated with a more significant decrease in LDL are consistent with the fact that larger MIs are associated with a more intense acute-phase and inflammatory response [15]. Similarly, patients with diabetes develop a more intense inflammatory response during the post-infarction recovery period compared to non-diabetics [16,17].

The fact that cholesterol levels decrease significantly after an acute MI is important clinically. It was recently shown that only about half the MI patients were prescribed high dose potent statin on discharge [18]; one of the factors found to predict lack of high dose potent statin prescription was LDL-C levels < 100 mg/dl [18]. It is important, therefore, to choose a statin type and dose not based on hospital LDL-C level taken more than 24 hours after admission for acute MI.

In conclusion, cholesterol levels decrease significantly after an acute MI, especially in larger infarctions associated with higher cTnT levels, and in diabetic patients. Measurements taken within 24 hours of onset may serve as a valid estimate of patient lipid profile and may be used to guide selection of lipid-lowering medication. Later measurements, however, may underestimate lipid levels and negatively influence clinical decisions.

Correspondence
Dr. D. Rott
Cardiac Rehabilitation Institute, Leviev Heart Center, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-8489
Fax: (972-3) 530-5905
email: david.rott@sheba.health.gov.il

References

1. Fyfe T, Baxter RH, Cochran KM, Booth EM. Plasma-lipid changes after myocardial infarction. *Lancet* 1971; 2: 997-1001.
2. Sniderman AD, Teng B. Predictable changes in low density lipoprotein composition after acute myocardial infarction. *Atherosclerosis* 1977; 27: 361-8.
3. Dupuis J, Tardif J-C, Cernacek P, Théroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation* 1999; 99: 3227-33.
4. Rauoof MA, Iqbal K, Mir MM, Tramboo NA. Measurement of plasma lipids in patients admitted with acute myocardial infarction or unstable angina pectoris. *Am J Cardiol* 2001; 88: 165-7.
5. Henkin Y, Crystal E, Goldberg Y, et al. Usefulness of lipoprotein changes during acute coronary syndromes for predicting postdischarge lipoprotein levels. *Am J Cardiol* 2002; 89: 7-11.
6. Fresco C, Maggioni AP, Signorini S, et al; LATIN Investigators. Variations in lipoprotein levels after myocardial infarction and unstable angina: the LATIN trial. *Ital Heart J* 2002; 3: 587-92.
7. Pitt B, Loscalzo J, Ycas J, Raichlen JS. Lipid levels after acute coronary syndromes. *J Am Coll Cardiol* 2008; 51: 1440-5.
8. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18: 499-502.
9. Alpert JS, Thygesen K, Antman E, Bassand JP. Infarction redefined – a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36: 959-69.
10. Schrott HG, Knapp H, Davila M, Shurzinske L, Black D. Effect of atorvastatin on blood lipid levels in the first 2 weeks of treatment: a randomized, placebo-controlled study. *Am Heart J* 2000; 140: 249-52.
11. Li JJ, Chen MZ, Chen X, Fang CH. Rapid effects of simvastatin on lipid profile and C-reactive protein in patients with hypercholesterolemia. *Clin Cardiol* 2003; 26: 472-6.
12. Pfohl M, Schreiber I, Liebich HM, Häring HU, Hoffmeister HM. Upregulation of cholesterol synthesis after acute myocardial infarction – is cholesterol a positive acute phase reactant? *Atherosclerosis* 1999; 142: 389-93.
13. Large V, Peroni O, Letexier D, Ray H, Beylot M. Metabolism of lipids in human white adipocyte. *Diabetes Metab* 2004; 30: 294-309.
14. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990; 82: 495-506.
15. Habib SS, Kurdi MI, Al Aseri Z, Suriya MO. CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome. *Arq Bras Cardiol* 2011; 96: 13-17.
16. Krasnodębski P, Opolski G, Karnafel W. Plasma adiponectin levels in acute myocardial infarction and during the postinfarction recovery period in patients with type 2 diabetes mellitus. *Kardiol Pol* 2011; 69: 924-30.
17. Choi KM, Lee KW, Kim SG, et al. Inflammation, insulin resistance, and glucose intolerance in acute myocardial infarction patients without a previous diagnosis of diabetes mellitus. *J Clin Endocrinol Metab* 2005; 90: 175-80.
18. Elis A, Pereg D, Dicker D, et al. Temporal trends in the use of high-dose potent statins following acute coronary syndrome in Israel. *Cardiology* 2014; 128: 266-72.